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REVIEW

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SARS-CoV-2: An immunogenetics call to arms

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Abstract

Susceptibility to viral infection, development of immunity, response to treatment and patient clinical outcomes are all under the control of heritable factors in the host. In the context of the current SARS-Cov-2 pandemic, this review considers existing immunogenetic knowledge of virus-immune system interactions. A major focus is to highlight areas in which work is required in order to improve understanding of antiviral immune responses and to move towards improved patient management.

1 | INTRODUCTION

Thucydides was a Greek Historian whose contemporary account of the plague of Athens (430BC) contains what is considered the first reference to the development of immunity following exposure to an infectious agent. He recognized the disease did not attack the same person a second time and that recovered individuals could provide support to those infected without concern for their own health.

SARS-CoV-2 is a modern day pandemic that has many parallels with Thucydides (a translation available at https://www.ancient.eu/article/1535/thucydides-on-the-plague-of-athens-text--commentar/ certainly has resonance with the situation we find ourselves in today).

Taking Thucydides' observation on the effect of a first infection in protecting against a second, in the year 2020 AD, as immunogeneticists, what more do we understand about this phenomenon and other aspects of immunity and how might that help us in management of the SARS-CoV-2 outbreak?

The contribution of the innate immune response to viral infection is well described (see review by Kikkert, 2020), and its role in defence against SARS-CoV-2 is beginning to be explored. A highly theoretical case for a role of innate immunity in protection against disease through activation of the innate immune sensor toll-like receptor 5 (TLR5) has been developed by Golonka et al. (2020). This proposes treatment with flagellin, a protein found in motile bacteria, to trigger receptor activation with downstream production of cytokines (IL-22 and IL18) and IFN-β, engaging the immune response and nonspecifically promoting antiviral immunity. The idea stems from the observation made by authors from the same group (Zhang et al., 2014) that flagellin-mediated TLR5 activation of dendritic cells caused elimination of rotavirus infection in mice. This effect has also been observed by others in the reduction of viral load in the lungs of influenza A-infected mice (Georgel et al., 2019). Whilst a clinical proof of efficacy remains to be provided, it is relevant to note that a stop codon polymorphism is described for TLR5 (TLR^{39STOP}) that renders it unable to mediate flagellin signalling and that is associated with increased susceptibility to pneumonia caused by *Legionella pneumophila* (Hawn et al., 2005).

Killer cell immunoglobulin-like receptor (KIR) polymorphisms are influential towards the functioning of Natural Killer (NK) cells, and the deterministic role of NK in acute viral infection has been well described. Reports of resistance and susceptibility to HIV infection have been linked with certain KIR profiles (Zwolińska et al., 2016). The finding of a lower frequency of activating receptors in patients with acute encephalitis compared to controls has been linked to a less efficient response of NK cells by this group (Tuttolomondo et al., 2018). An association of severe influenza A (H1N1) 2009 infection with KIR gene content again implicating NK cell function has been likewise described by Aranda-Romo et al. (2012). The relationship between KIR/NK and SARs-Cov-2 has not been explored beyond observations regarding relative NK frequency noted below and represents an outstanding area of research need.

A considerable body of evidence identifies that the polymorphism of human leucocyte antigens (HLA) has resulted from the selective pressure from infectious diseases. From this work, it is well established that susceptibility to infectious disease, the capacity to mount a protective immune response and, ultimately, clinical outcome are all informed by HLA genes. In modern times, these influences are most often observed in inter-individual responsiveness to vaccination. Associations with natural infection have, however, been reported. Most notably in the context of the current article, an increase of HLA-B*46:01 allele frequency was

identified in a probable SARS-infected Taiwanese population that reached significance in the "severe cases" patient group (Lin et al., 2003). Similarly, an association with HLA-B*07:03 and susceptibility to SARS infection in a Hong-Kong Chinese population (Ng et al., 2004) has been defined, and susceptibility with HLA-DRB1*12:02 in a Vietnamese population also reported (Keicho et al., 2009). Others have, however, reported absence of any HLA association with SARS (Yuan et al., 2014). Protection from infection has also been reported (Ng et al., 2004). A more comprehensive account of HLA studies in the context of coronavirus infection is provided in the recent publication by Sanchez-Mazas (2020) which also highlights the error in some publications arising from weak study design and data handling.

Taken together, these observations identify a differential susceptibility to infection and outcome that has resulted in advice that individuals with HLA-susceptible genotypes should be shielded (Ng et al., 2004). A heritable susceptibility to infection is further reinforced in the twin study reported by Williams et al. (2020) that links symptomatic infection with SARS-CoV-2 to a predisposing genetic background, although this is not further defined. In this edition of IJI, we report HLA-DR and -DQ associations with infection in a SARS-CoV-2-positive renal patient group (Poulton, 2020).

At the time of writing, we have a very incomplete understanding of the adaptive immune response to SARS-CoV-2 infection. The humoural arm is, for the moment, the better represented aspect in the literature reflecting established routine antibody testing programmes. Zhou et al. (2020) have identified the development of an IgM response, followed by IgG at week two. Very importantly, they show that for some patients, antibody-containing sera could prevent virus entry to target cells, meaning that immunity to re-infection had been gained. Long et al. (2020) show that in their series of 285 patients, the proportion of patients with SARS-CoV-2 IgM reached a peak of 94% between twenty and twenty-two days after symptom onset, whilst 100% of patients became IgG positive within seventeen to nineteen days post-infection. Both IgM and IgG levels plateaued within six days after seroconversion. Response extent and dynamics in different HLA subpopulations have not yet been investigated, but from work done in other viral infections, the HLA background would be expected to exert an influence. For example in cytomegalovirus infection, Ishibashi et al. (2009) have shown a relative paucity of the antiviral antibody response amongst HLA-DR10 and DR11 subjects compared to others and identify that, in respect of DR11, a correlate exists in terms of susceptibility to active CMV infection reported by others (Fan et al., 2006).

Research on cellular responsiveness to SARS-CoV-2 is lagging behind that on humoural immunity but is beginning to accumulate. Much of this is narrative in nature, describing changes in frequency of cell subsets based on flow cytometric analysis. These describe various perturbations in subset frequencies that include increased percentages of HLA-DR and CD38 double-positive populations (Xu et al., 2020), a phenotype generally associated with T-cell activation. This finding is paralleled in other viral infections and has been reported to be associated with severe disease in patients dying of influenza viral infection (Wang et al., 2018). Most recently, Wang et al. (2020) have reported a decrease in absolute numbers of T and B cells with concomitant increase in HLA-DR/CD45 RO expression and increased percentage of interferon gamma producing CD8+ cells in severe and extremely severe patients compared with mild patients. Ni et al. (2020) have identified an increased frequency of NK cells in convalescent patients and T-cell production of interferon gamma as a marker for development of a SARS-CoV-2-specific T-cell response.

An intriguing feature of the response to SARS-CoV infection reported in the detailed molecular study by Josset et al. (2013) is that in contrast to another coronavirus, HcoV-EMC, SARS-CoV caused upregulated expression of the majority of genes within the antigen presentation pathway, including both HLA-CI and CII. The transcriptional response to SARS-CoV-2 has been described in the paper by Blanco-Melo et al. (2020). Although it omits consideration of HLA, this identifies a transcriptional signature that, compared to that of influenza and respiratory syncytial virus, is deficient in respect of reads that map to certain cytokines including type I and type III interferons and several chemokines. The association of certain cytokine gene polymorphisms with SARS-CoV has also been identified by others. The IFN-gamma +874A allele and RANTES -28 G allele are risk factors for susceptibility, and the RANTES -28G allele also has a role in pathogenesis (Lau & Peiris, 2009). These findings clearly identify genomic profiling as a powerful tool towards rapid characterization of emerging viruses that enables identification of possible treatment strategies.

The severe deterioration of some patients with SARS-CoV-2 infection has been linked with the occurrence of a cytokine "storm." This entails the overproduction of tumour necrosis factor [TNF], IL-6 and IL-1β with risk for multiorgan failure and death. Whilst the drivers of this event are debated, it cannot be overlooked that for each of the implicated cytokines, gene polymorphisms linked to high and low producer phenotypes have been described. Those individuals with a high producer genotype might therefore, a-priori, be considered to represent a higher risk group of patients when presenting with initial symptoms of illness and warrant risk-adjusted management from the outset. Justification for this suggestion can be found in the SARS-CoV literature that links specific clinical outcomes and sequelae of infection with particular polymorphisms (Chong et al., 2006; Wang et al., 2008).

The development of a SARS-CoV-2 vaccine is a core strategy towards pandemic arrest. In seeking an effective vaccine, the identification of potential T- and B-cell epitopes using in-silico tools provides a means to expedite the development process. Using this approach, Fast, Altman, and Chen (2020) have identified more than four-hundred viral peptides with good antigen presentation scores for MHC-CI and CII and a subset of thirteen of these as the "top" potential epitopes based on good coverage of presentation by MHC-CI and CII alleles and candidacy as a B-cell epitope. Using a similar approach, Nguyen et al. (2020) have performed analysis of SARS-CoV-2 peptide/MHC-CI binding affinity across 145 different HLA types. This has allowed ranking of alleles in regard to their capacity to present peptides from the SARS-CoV-2 proteome and for

TABLE 1 Collaborative projects focused on genetic aspects of SARS-CoV-2 infection

Project	Aims	Details
18th International HLA and Immunogenetics Workshop: Covid-HLA-Genome (COHLAGE)	Definition of HLA associations with disease.	https://www.ihiw18.org/component-immunogenetics/project-covid-hla-genome-cohlage/
GenOMMIC	Definition of genetic susceptibility to coronavirus	https://www.genomicsengland.co.uk/genomics-england-genomicc-nhs-covid-19/
The Covid-19 Host Genetics Initiative	Promotion of data sharing and collaborative working	https://www.covid19hg.org/

Note: Thucydides may have a modern day counterpart in our midst.

development of a global susceptibility map based on population allele frequencies. Whilst the authors caution that until their findings are clinically validated they should not be used to inform clinical decision-making, they do recommend incorporation of HLA testing into clinical trials and pairing of HLA typing with SARS-CoV-2 testing.

Treatments for SARS-Cov-2 are being actively sought with more than 500 modalities currently in trial (Thorlund et al., 2020). A number of agents bring about their effects through inhibition of cytokine signalling pathways to reduce pro-inflammatory activity and abrogate the cytokine storm syndrome. Amongst these, the IL-6-blocking antibody toclizumab has been the subject of interest in a number of reports (Di Giambenedetto et al., 2020; Zhang, Wu, Li, Zhao, & Wang, 2020) and ongoing off-label trials. Toclizumab exerts its effects through targeting IL-6 receptors (IL6R) and has proven to be a highly effective treatment in rheumatoid arthritis (RA). In this setting, however, clinical response is variable and has been shown to be associated with an IL6R gene SNP (rs12083537), patients with the homozygous AA genotype showing a significantly better response than homozygous or heterozygous patients with the G allele (Luxembourger et al., 2019). Anakinra an IL-1 receptor antagonist with potential for therapeutic use in SARS-CoV-2 infection and currently used in treatment of systemic juvenile idiopathic arthritis (sJIA) has similarly been shown to exhibit differential effectiveness (Stock et al., 2008) that the authors considered may be linked to a IL1 receptor SNP.

Allelic variants of viral receptors have been demonstrated to link with differential binding and host susceptibility (Ohtsuka & Taguchi, 1997). It is of potential importance then that angiotensin-converting enzyme 2 (ACE2), the gene for the receptor for SARS-CoV-2, has been shown to exhibit polymorphism. Whilst entry of the closely related SARS-CoV into human host cells does not appear associated with ACE2 genotype, variation in the intermolecular interaction of the SARS-Cov-2 spike protein with ACE-2 variants has been identified through in-silico modelling (Hussain et al., 2020). The possibility is then raised that a proportion of the population may be incapable of becoming infected by virtue of their expression of a nonpermissive (for viral attachment) variant form. This contention is, however, disputed by Cao et al. (2020) whose data, based on analysis of large scale genome databases, fail to support existence of SARS-Cov-2 binding-resistant ACE2 polymorphisms in different East Asian populations. There is clearly a requirement for real-life data to address this urgent question.

Whilst we have so far considered the influence of HLA on viral immunity, it must not be overlooked that the relationship of HLA with viral infection may reflect a direct role of the relevant allele as a virus receptor. In this regard, a role for HLA-C in infection with HcoV-HKU1 has been defined (Chan et al., 2009). By modification of the nonpermissive kidney cell line BHK21 using a cDNA library from the fully permissive lung epithelial cell line A549, these authors were able to demonstrate binding of purified virus spike protein to HLA-Cw. Binding could be blocked by SiRNA silencing and with HLA-Cw antibody. However, in a further nonpermissive cell line, NIH-3T3, HLA-C expression did not make the cell susceptible to infection implying that HLA-Cw was more likely to be a co-receptor for cellular entry. Although the paper from Wu and Zheng (2020) reporting the finding that the angiotensin-converting enzyme 2 (ACE2) receptor for SARS-Cov-2 tends to be co-expressed with HLA-DRB1 is of interest in this regard, the authors do not explore the relationship of expression to infection.

What the above underlines is the need for immunogenetic due-diligence in development of our understanding of SARS-Cov-2, SARS-Cov-2-host interaction and in development of SARS-Cov-2 treatment strategies. Our inputs into the considerable research efforts being expended are essential in defining where our genes may gain us protection or render us vulnerable. In this regard, the efforts of the international scientific community have recently begun to coalesce around a number of projects as identified in Table 1 a

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